IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

LEWIS et al. Atty. Ref.: 4371-4

Serial No. 09/284,009 Group: 1636

Filed: April 5, 1999 Examiner: Qian

For: MONONUCLEAR PHAGOCYTES IN THERAPEUTIC DRUG DELIVERY

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August 11, 2003

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

RESPONSE/SUBMISSION

Responsive to the Official Action dated March 11, 2003, and pursuant to the Submission requirement of 37 CFR § 1.114, consideration of the following remarks and return of an initialed copy of the attached PTO 1449 Form, pursuant to MPEP § 609) are requested. The cited documents were submitted with the Response of June 11, 2003 and further copies of the same are not believed to be required.

The period for response has been extended up to and including August 11, 2003, by submission of the attached two month extension fee and petition.

A Request for Continued Examination (RCE) is attached and withdrawal of the finality of the Office Action of March 11, 2003 is also requested.

The undersigned submits that the Response of June 11, 2003 should be a sufficient Submission, as described in MPEP § 706.07(h) (Rev. 1, Feb 2003, p 700-84)

however out of an abundance of caution, the arguments presented therein are submitted herein along with a new request for at least a telephonic interview in the event the Examiner continues to find the evidence unpersuasive and a PTO 1449 Form listing the previously provided art.

An interview with the Examiner is requested, at least by telephone, in the event the following arguments are found unpersuasive. The Examiner is requested to contact the undersigned to arrange the same at a time convenient to the Examiner's schedule, prior to issuance of a further Action on the merits.

The Section 112, first paragraph, rejection of claims 87-93, 101, 104, 109-116 and 120-125 is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following comments as well as the previously submitted evidence.

The presently claimed invention provides mononuclear phagocytes modified to contain at least one hypoxia and/or ischemic and/or stress regulatable element operably linked to at least one nucleotide sequence or interest (NOI) and a use and methods of treating targeting a mononuclear phagocyte to hypoxic and/or ischemic and/or stress sites, methods of treating a condition associated with a hypoxic and/or ischemic and/or stress state as well as a method for selectively destroying a mononuclear phagocyte and a delivery system containing the mononuclear phagocyte.

The only outstanding rejection appears to be based on the Examiner's belief that one of ordinary skill in the art would not have been able to use the claimed invention from a teaching of the specification and the generally advanced level of skill in the art. Specifically, the Examiner indicates that while the specification demonstrates that

macrophages infiltrate tumor sites in mice and express a marker gene, such as GFP or ß-gal, "the specification fails to teach whether a therapeutic gene can be expressed at high and sustained level that is capable of achieve [sic] a therapeutic effect." See, page 3 of the Office Action dated March 11, 2003 (Paper No. 19). The Examiner also states that "the *in vitro* testing provided by the specification and the Naylor Declaration [i.e. Declaration of Stuart Naylor, Ph.D. executed April 24, 2002] only demonstrate the expression of marker gene instead of a gene that can achieve a therapeutic effect". See, page 4 of Paper No. 19. The Examiner concludes that it is unpredictable whether a mononuclear phagocyte can deliver a drug, such as a therapeutic gene, to a hypoxic site and achieve a therapeutic effect. The applicants respectfully disagree with the Examiner's conclusion as to unpredictability of using the presently claimed invention and urge consideration of the following and the previously submitted evidence in this regard.

Initially, the applicants note that Dr. Naylor is certainly qualified to opine on the level of ordinary skill in the art and the predictability or unpredictability of delivery of therapeutic components, in place of the exemplified marker genes, using the presently claimed invention. In this respect, the applicants note that Dr. Naylor has specifically commented that, in his opinion, the data described in Examples 1 and 2 of his Declaration clearly support that the methods and results described in the present application are enabling in an *in vivo* situation and that one of ordinary skill in the art would have been able to make and use the claimed invention, without undue experimentation, at the time the claimed invention was made. See, page 6 of the Naylor Declaration. Dr. Naylor specifically indicates that the replacement of a reporter

gene with a therapeutic gene would have been a matter of routine experimentation for one of ordinary skill in the art. Id. Dr. Naylor refers in this regard to U.S. Patent No. 6,265,390, which teaches construction of HRE-marker gene constructs and HRE-prodrug constructs, and the subsequent use thereof for hypoxically-regulated expression. Dr. Naylor also notes that the present specification exemplifies the construction of adenoviral vectors containing HRE-lacZ and adenoviral vectors containing HRE-IL2 in Example 2. A copy of the indicated U.S. Patent No. 6,265,390, has been previously submitted for the Examiner's convenience and consideration. Dr. Naylor has also provided as a part of his Declaration a demonstration that macrophages express HIF-1α when exposed to hypoxia *in vitro* or in avascular areas of human tumors, human wounds and human arthritic joints. See, Figures 4, 5 and 6 as well as pages 7 and 8 of the Naylor Declaration.

Dr. Naylor summarizes these results as providing evidence that hypoxic conditions can induce the activity of hypoxia inducible transcription factors, such as hypoxia inducible factor-1 (HIF-1), which is capable of binding to cognate DNA recognition sites, the hypoxia-response elements (HREs) and upregulating the expression of a gene associated with the HRE.

Dr. Naylor specifically concludes, as one of skill in the art, that the data provided in the Declaration clearly supports that a mononuclear phagocyte that has coupled thereto, or internalized therein, a hypoxia and/or ischemic and/or stress regulatable agent can localize and express a gene of interest at a target site. See, page 8 of the Naylor Declaration.

The applicants respectfully submit that the Naylor Declaration is persuasive and conclusive as to the predictability of the use of mononuclear phagocyte to deliver a drug, or therapeutic gene, to a hypoxic site to achieve a therapeutic effect. The Examiner has not indicated where Dr. Naylor's conclusions are inconsistent with the expectations of one of ordinary skill or are scientifically or technically unsound. It is the Examiner's burden to provide evidence or technical reasoning substantiating any doubts that a disclosure is not enabled. See MPEP 2164.04. Without a reason to doubt the truth of the statements made in the patent application, the application must be considered enabling. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). See MPEP Section 706.03 for guidance with respect to the Examiner's burden under the enablement requirement. As such, the case law supports that properly reasoned and supported statements explaining any failure to comply with Section 112 are a requirement to support a rejection. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

Notwithstanding the above, the ability of a mononuclear phagocyte to target hypoxic or ischemic sites is further demonstrated by U.S. Patent No. 6,379,647 (copy previously).

Moreover, the specification teaches that nucleotide sequences of interest include nucleotide sequences encoding prodrug activation enzymes, (see, page 9, lines 23-24), nucleotide sequences encoding cytokines (page 15, lines 15-21 of the specification), and nucleotide sequences encoding antibody molecules (pages 40 and 41 of the specification). As confirmed by Dr. Naylor, and discussed above, the applicants believe

one of ordinary skill in the art would have been able to produce therapeutic levels of, for example, nucleotide sequences encoding pro-drugs and/or cytokines, for example, in diseased tissues, such as tumor tissue, without undue experimentation.

In further support of this belief, the applicants previously submitted Nishihara et al. (Endocrinology (1997) vol. 138, No. 11, pp. 4577-4583) wherein HSV-tk expression was correlated from *in vitro* to *in vivo* upon ganciclovir treatment. Specifically, Nishihara teaches the well-known use of herpes simplex virus thymidine kinase (HSV-tk) "as the most widely used suicide gene". See, right column, lines 8-9 of page 4577 of Nishihara. Nishihara explains that HSV-tk converts the antiviral prodrug of nucleotide analogs such as ganciclovir (GCV) and acyclovir to the monophosphorylated form, which is then converted to the toxic triphosphate forms by endogenous cellular kinases that compete with normal nucleotides for DNA replication. "[T]he Expression of HSV-tk gene in mammalian cells renders them sensitive to GCV, thereby killing them by interfering with DNA synthesis." See, page 4577 of Nishihara et al. Nishihara also described the well-known "bystander effect" and radiosensitization as two additional advantages of HSV-tk/GCV therapy. Id. and the Discussion section. Clearly, one of ordinary skill would have reasonably expected that the HSV-tk gene described by Nishihara et al. could have been delivered, without undue experimentation, as a nucleotide sequence of interest to a hypoxic site, an ischemic site and/or a stress site, by a mononuclear phagocyte of the presently claimed invention, under regulatory control of a hypoxia regulatable element, an ischemic regulatable element and/or a stress regulatable element, and used with GCV, as described in Nishihara et al.

The presently claimed invention provides cells and methods of making the cells. As such, it would have been predictable to one of ordinary skill in the art to use mononuclear phagocyte modified to include a nucleotide sequence of interest such as a pro-drug activation enzyme, to provide a therapeutic benefit in an injured tissue, such as a tumor, particularly in view of the present specification and the Naylor Declaration, as well as the previously submitted U.S. Patent No. 6,379,647 which teach that mononuclear phagocyte home to or target hypoxic or ischemic injured tissue. In addition, and in response to the Examiner's comment relating to "high and sustained level" of expression of the nucleotide sequence of interest, the applicants note that screening cells *ex vivo* for levels of expression is a matter of routine experimentation.

The applicants further urge the Examiner to consider the previously submitted Kluth et al. reference (The Journal of Immunology, (2001) 166:4728-4736) which teaches expression of IL-4 from transfected macrophages and use of the same for the reduction of inflammation in glomerulonephritis. Kluth et al. therefore demonstrate that macrophages transfected with adenovirus expressing rat IL-4 (Ad-IL4) localize to inflamed glomeruli and that they reduce the severity of injury in rats with experimental glomerulonephritis. See, page 4729, left column, first paragraph of Kluth et al.

Interestingly, Kluth et al conclude as follows: "Our data highlight the fact that macrophage transfection provides an effective method to deliver genes and express biologically active molecules in glomeruli, a target that has proved difficult using convention viral and nonviral methods." See, page 4733, right column, first full paragraph of Kluth et al. Kluth et al. therefore confirms that the use of an embodiment of the presently claimed invention did not require undue experimentation. With respect

to cytokine gene therapy, Kluth et al. demonstrate that success of the macrophage targeted IL-4 therapy was consistent with, and therefore predictable from, the state of the art for IL-4 gene therapy. See, page 4735, left column, 3rd paragraph.

The specification and the Naylor Declaration, as well as the previously submitted documents, demonstrate that mononuclear phagocytes of the claimed invention are useful and may be used, without undue experimentation, for delivering a nucleotide sequence of interest. The homing mechanism of action of a mononuclear phagocyte containing an hypoxia, ischemic or stress regulatable element may be used for targeting diseased tissue, such as a tumor or cardiovascular tissue, for example. As such, the presently claimed invention may be used for delivering a nucleotide sequence of interest to target tissue in an animal, i.e., for cancer, diabetic retinopathy, cardiovascular disease, arthritis, glomerulonephritis, or other diseases involving injured tissue having ischemic, hypoxic or stress sites.

The Examiner has found the above-presented arguments unpersuasive for the reasons noted in the Advisory Action dated July 24, 2003. Essentially, the Examiner asserts that the post-filing evidence carries little or no weight in considering the enabling support of the present specification. The Examiner is urged to appreciate however that the MPEP allows for an applicant to rely on such art, as provided by the applicants. Specifically, the Examiner is requested to appreciate that the MPEP provides the following:

> "While a later dated publication cannot supplement an insufficient disclosure in a prior dated application to make it enabling, applicant can offer the testimony of an expert based on the publication as evidence of the level of skill in the art at the time the application was filed. *Gould v. Quigg*, 822 F.2d

1074, 1077, 3 USPQ2d 1302, 1304 (Fed. Cir. 1987)." See, MPEP § 2164.05(b).

The applicants have provided a Declaration of Dr. Naylor with a discussion of art as indicated above in support. Reliance of the same is appropriate and should be persuasive, according to the above-quoted section of he MPEP.

In view of the above and previously submitted documents therefore, the applicants submit that the claimed invention could have been used, without undue experimentation. The Section 112, first paragraph, rejection of the claims should be withdrawn.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

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